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Benign atypical intravascular CD30+ T-cell proliferation: a recently described reactive lymphoproliferative process and simulator of intravascular lymphoma: report of a case associated with lichen sclerosus and review of the literature

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Abstract: Objectives: Intravascular accumulations of atypical large lymphoid cells are a rare finding in skin biopsy specimens and raise the suspicion for intravascular lymphoma. The intravascular accumulation of atypical large CD30+ T cells, however, as a reactive process is very uncommon in the skin, with only four cases documented so far in the literature. This condition, referred to as benign intravascular atypical CD30+ T-cell proliferation, has been associated with chronic inflammation after trauma. **Methods:** We report on a case of atypical intravascular CD30+ T-cell proliferation in a patient with ulcerated lichen sclerosus on the foreskin, discuss the differential diagnoses, propose diagnostic criteria, and review the literature on this uncommon reactive intralymphatic CD30+ T-cell lymphoproliferation. **Results:** The atypical intravascular CD30+ T-cell proliferation is characterized by the accumulation of large CD30+ polyclonal T cells within lymphatics in close vicinity to ulceration or an inflammatory skin disease. There is no association with Epstein-Barr virus infection. **Conclusions:** This benign cutaneous lymphoproliferation needs to be distinguished from intravascular T-cell lymphoma, particularly from the intravascular variant of anaplastic large cell lymphoma. Obstruction of lymphatics due to lichen sclerosus with disrupted immune cell trafficking may result in the accumulation of activated CD30+ lymphocytes.

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Benign Atypical Intravascular CD30+ T-Cell Proliferation: A Recently Described Reactive Lymphoproliferative Process and Simulator of Intravascular Lymphoma

Report of a Case Associated With Lichen Sclerosus and Review of the Literature

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Key Words: CD30; T-cell; Lymphoproliferation; Intravascular; Benign; Atypical; Lymphoma; Skin

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ABSTRACT

Objectives: Intravascular accumulations of atypical large lymphoid cells are a rare finding in skin biopsy specimens and raise the suspicion for intravascular lymphoma. The intravascular accumulation of atypical large CD30+ T cells, however, as a reactive process is very uncommon in the skin, with only four cases documented so far in the literature. This condition, referred to as benign intravascular atypical CD30+ T-cell proliferation, has been associated with chronic inflammation after trauma.

Methods: We report on a case of atypical intravascular CD30+ T-cell proliferation in a patient with ulcerated lichen sclerosis on the foreskin, discuss the differential diagnoses, propose diagnostic criteria, and review the literature on this uncommon reactive intralymphatic CD30+ T-cell lymphoproliferation.

Results: The atypical intravascular CD30+ T-cell proliferation is characterized by the accumulation of large CD30+ polyclonal T cells within lymphatics in close vicinity to ulceration or an inflammatory skin disease. There is no association with Epstein-Barr virus infection.

Conclusions: This benign cutaneous lymphoproliferation needs to be distinguished from intravascular T-cell lymphoma, particularly from the intravascular variant of anaplastic large cell lymphoma. Obstruction of lymphatics due to lichen sclerosis with disrupted immune cell trafficking may result in the accumulation of activated CD30+ lymphocytes.

The presence of intravascular large atypical lymphocytes raises the suspicion for intravascular lymphoma (IVL) or leukemia. IVL is an aggressive disease, which most commonly represents a diffuse large B-cell lymphoma with predominantly intravascular growth, but a very rare T-cell variant has been described, including cases with expression of CD30 by tumor cells.¹⁻⁵ On the other hand, primary cutaneous CD30+ lymphoproliferative diseases (CD30+ LPDs) encompass a spectrum of diseases such as lymphomatoid papulosis (LyP), primary cutaneous anaplastic large-cell lymphoma (ALCL), and so-called borderline lesions, with all exhibiting an excellent prognosis.⁶⁻⁸ The tumor cells in CD30+ LPDs mostly are large pleomorphic or anaplastic T cells. The expression of CD30, however, is not restricted to lymphomas. An increasing number of reactive conditions are known to harbor atypical medium- to large-sized CD30+ T cells, such as infestations, viral infections, and drug eruptions.^{6,9} Recently, benign proliferation of intravascular atypical CD30+ T cells as a reactive process due to trauma was described, but so far, only a few cases have been reported.^{10,11} We present a case of benign atypical intravascular CD30+ T-cell proliferation occurring in a patient with focally ulcerated lichen sclerosis (LS) on the foreskin and review the literature on this reactive lymphoproliferation, which may mimic IVL.

Case Report

A 46-year-old man had LS with white, sclerotic, focally eroded areas (up to 1 cm in diameter) on the prepuce, which slowly had increased to 7 cm in diameter over several months, before seeking treatment at the department of urology to

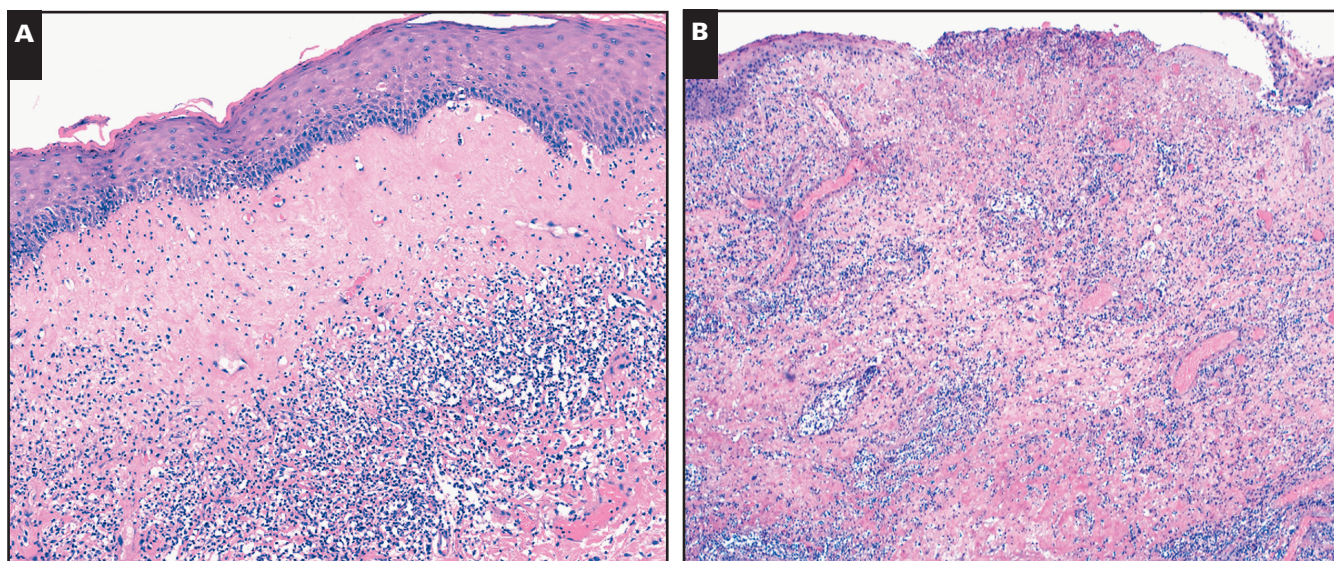


Image 1 **A**, Lichen sclerosus et atrophicus on the prepuce with vacuolization of the junctional zone, subepidermal hyalinized collagen tissue, and a predominantly lymphocytic infiltrate (H&E, $\times 100$). **B**, Focal epidermal ulceration and enlarged thin-walled vessels filled with lymphoid cells in the underlying dermal tissue (H&E, $\times 25$).

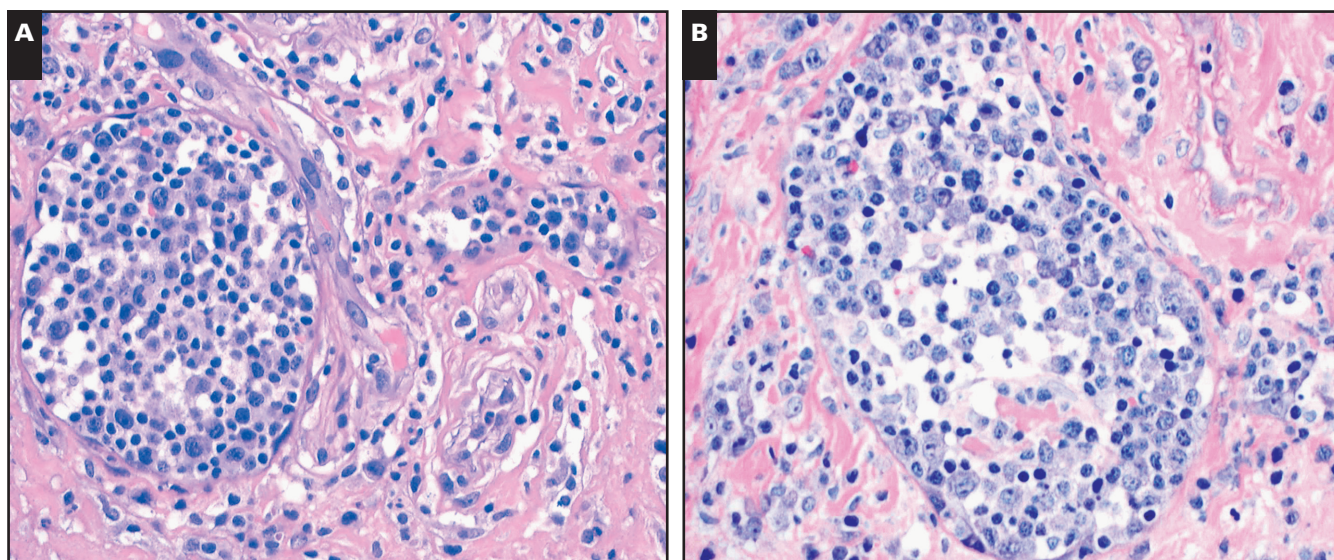


Image 2 The intravascular lymphoid cells encompass medium- to large-sized cells demonstrating pleomorphic nuclei with finely dispersed chromatin, prominent to small nucleoli, and a moderate amount of cytoplasm, some with mitosis and intermingled small lymphocytes with chromatin-dense nuclei (**A**, H&E, $\times 400$; **B**, Giemsa, $\times 400$).

undergo circumcision. His medical history showed no chronic disease or long-term medications.

The histologic examination of the prepuce showed the characteristic features of LS with vacuolization of the junctional zone, subepidermal hyalinized collagen tissue, and a band-like predominantly lymphocytic infiltrate **Image 1A** and **Image 1B**. The lymphocytes were small sized, with chromatin-dense nuclei lacking atypia, and were admixed with a few slightly enlarged lymphocytes. At scanning magnification, thin-walled ectatic vessels filled

with medium- to large-sized blasts were discernible in the superficial dermis **Image 2A** and **Image 2B**. These large lymphoid cells displayed pleomorphic and slightly polymorphic nuclei containing small and occasional large nucleoli and showed a moderate eosinophilic cytoplasmic rim, staining basophilic with the Giemsa stain. Occasionally, similar lymphoid cells expanded in the perivascular tissue admixed to some histiocytes, plasma cells, and rare eosinophils. Subtle erythrocyte extravasation but no vasculitic changes were present. Immunohistochemical analysis demonstrated that the

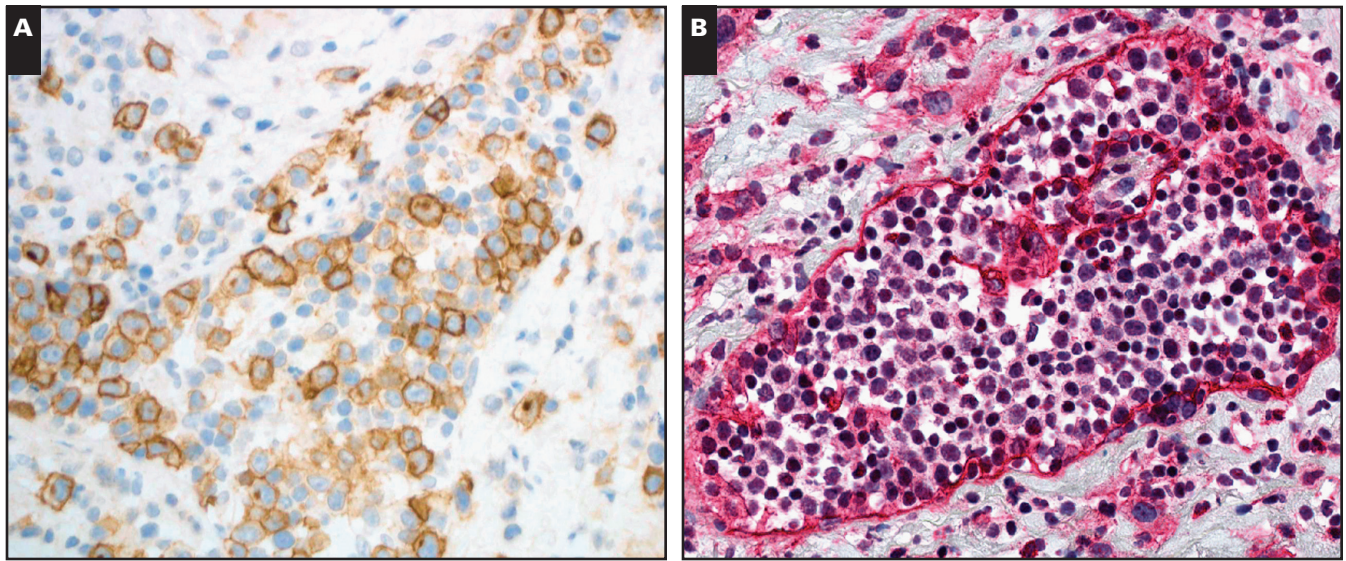


Image 3 **A**, Immunophenotype of intravascular lymphocytes that express CD3, CD4, and CD30 with 90% of the cells being positive for the latter antigen (×400). **B**, Expression of CD3, CD4, and a partial loss of CD7 expression (approximately 30% of the cells) as well as negativity for CD20. Expression of podoplanin by the endothelial cells lining the ectatic vessels (×400).

intravascular atypical medium- to large-sized lymphocytes expressed CD2, CD3, CD4, CD5, and CD45, with partial expression of CD7 and with concomitant expression of CD30 in 90% of the cells **Image 3A**. Anaplastic lymphoma kinase 1 (ALK-1), epithelial membrane antigen (EMA), CD1a, CD56, and CD43 were not expressed. B-cell markers, including CD20 and CD79a, were consistently negative. Epstein-Barr virus–encoded small RNA (EBER) in situ hybridization (ISH) was negative. The endothelial cells lining the ectatic vessels were positive for CD31 and podoplanin and negative for CD34 **Image 3B**, indicating lymphatic vessels. T-cell receptor (TCR) γ genotyping using specific polymerase chain reaction (PCR) (Vg1-8, Vg9, Vg10-12, Jg1/2, JgP1/2, and JgP primers) and fragment analysis as well as PCR-based clonality assays using a BIOMED2 protocol revealed a polyclonal T-cell population.¹²

Since clinical examination was unremarkable, without any signs of extracutaneous lymphoma, and peripheral blood leukocyte counts did not reveal leukemia, a wait-and-see strategy was suggested. During the follow-up period of 21 months, the health status of the patient was unremarkable, with no signs of lymphoma or leukemia or episodes of fever or weight loss. Blood tests at diagnosis and during follow-up were normal.

Discussion

Intravascular accumulations of atypical large lymphoid cells are a rare finding in skin biopsy specimens and raise the suspicion for IVL. Most cases of IVL are of B-cell origin

and represent a form of diffuse large B-cell lymphoma, with a predominantly intravascular proliferation of tumor cells.¹³ A subset of IVL is of T-cell origin. In a series of 50 cases of intravascular large natural killer (NK)-cell and T-cell lymphomas, the tumor cells were positive for T-cell markers CD2 and CD3 and, in most cases, for the NK-cell marker CD56.¹ Furthermore, the cells expressed cytotoxic proteins, and in most cases, EBER could be detected by ISH. The phenotype resembled that of extranodal NK-/T-cell lymphoma, nasal type. Clinically, IVL displays erythema nodosum-like lesions, painful telangiectasias, or livedo racemosa skin lesions.¹⁴ The prognosis of IVL, independent of T- or B-cell origin, is unfavorable, with a 3-year survival rate of 33% for the systemic form of IVL and a relatively better prognosis in its cutaneous form. Expression of CD30 is usually not present in IVL but is a consistent and defining feature of intravascular ALCL (IV-ALCL). So far, fewer than 10 cases of IV-ALCL have been documented in the literature, including four cases restricted to the skin²⁻⁵ and two patients with secondary cutaneous involvement by systemic ALCL.^{15,16} In contrast to T-cell IVL, IV-ALCL expresses CD4 and CD30 but is negative for cytotoxic markers and EBER. Expression of ALK-1 and EMA, which is a common finding in systemic ALCL, is rarely present in IV-ALCL. Monoclonal rearrangement of TCR γ genes was documented in some cases of IV-ALCL. Clinically, IV-ALCL manifests with patches and plaques or nodular lesions.^{3,4} The data on the prognosis of IV-ALCL are heterogeneous and do not allow drawing stringent conclusions. In addition to IV-ALCL, the angioinvasive form of LyP (referred to as LyP type E) has to be included in the differential diagnosis.¹⁷ In this variant

■Table 1■

**Cutaneous Benign Atypical Intravascular CD30+ T-Cell Proliferation:
Clinicopathologic Features of the Cases Reported in the Literature and the Presented Case**

Case	Sex/Age, y	Location	Clinical Presentation	Staging	Phenotype	TCR	Therapy	Follow-up
Baum et al, 2009 ¹⁰	M/17	Right forearm	Seven- to 8-week history of a 1.7 × 1.3-cm erythematous patch with central erosion and peripheral collarette of scale after trauma	Negative (blood)	CD4+ (60%), CD30+	Oligoclonal	SE	CR, NR 8 mo
Ardighieri et al, 2010 ¹⁸	F/69	Arm	Solitary lesion (diameter: 10 mm) on the arm, clinically diagnosed as pyogenic granuloma and removed by shave biopsy	Negative	CD4+, CD30+	Polyclonal	Shave biopsy	CR, NR 9 mo
Riveiro-Falkenbach et al, 2013 ¹¹	M/45	Trunk	Few-week history of a 2.5-cm ulcerated cutaneous nodule on the trunk	Negative	CD4+, CD30+	Polyclonal	RT	CR, NR 23 mo
Riveiro-Falkenbach et al, 2013 ¹¹	F/17	Neck	Four-month history of ulcerated and exophytic cutaneous laterocervical lesion developed after a trauma	NA	CD3+, CD30+	NA	Shave biopsy	CR, NR 24 mo
Present case	M/46	Prepuce	Ulcerated hypopigmented lesion on the prepuce of less than 1 cm in diameter	Negative	CD4+, CD30+	Polyclonal	SE	CR, NR 21 mo

CR, complete remission; NA, no data available; NR, no recurrence; RT, radiotherapy; SE, surgical excision; TCR, T-cell receptor γ gene rearrangement analysis.

of LyP, dermal and subcutaneous vessels are infiltrated and destroyed by medium- to large-sized atypical CD30+ cells, resulting in dermal necrosis and hemorrhage. In some cases, the atypical cells may occlude the vessel lumina. The infiltration and destruction of vessel walls and extensive hemorrhage allow distinction of LyP type E from benign atypical intravascular CD30+ T-cell proliferation.

The atypical cytomorphology of the intravascular large CD30+ cells in our patient is at first glance suggestive of IVL. However, the context of an inflammatory skin disease with ulceration and the absence of other signs or symptoms of lymphoma, particularly the indolent clinical course, argue against malignancy and suggest a reactive intravascular T-cell proliferation in the context of a focally ulcerated LS. So far, only three cases of intravascular atypical large CD30+ cell proliferation have been documented ■Table 1■.^{10,11} The first case was a 17-year-old male patient described by Baum and coworkers,¹⁰ who observed an intravascular proliferation of CD30+ T cells in the context of a dermal inflammatory infiltrate after a trauma on the arm. Recently, Riveiro-Falkenbach et al¹¹ reported two patients with intravascular atypical CD30+ T cells. The first patient, a 45-year-old man, had a 2.5-cm ulcerated cutaneous nodule on the trunk. The second was a 17-year-old female patient with a 4-month history of an ulcerated and exophytic cutaneous laterocervical lesion having developed after a trauma. These

reports demonstrate that trauma with destruction of the epidermal layer represents a major trigger factor for the accumulation of large CD30+ T cells in superficial vascular channels. To our knowledge, we describe the first case of benign atypical intravascular CD30+ T-cell proliferation occurring in an (ulcerated) area of LS representing a chronic autoimmunologic skin disease. The repertoire of homing factors for these activated intravascular T cells in benign intravascular T-cell proliferations is widely unknown. In one report, CCR7 was expressed by reactive intravascular T cells, but less than 5% of the intravascular T cells expressed CD30 antigen in that case.¹⁸ CD30 is a transmembrane glycoprotein representing a member of the tumor necrosis factor receptor superfamily and plays a role in regulating the function or proliferation of normal lymphoid cells.¹⁹ CD30 is physiologically expressed by activated lymphoid cells and is observed in many inflammatory cutaneous diseases, usually affecting a small number of stimulated and histologically enlarged T cells. Reactive conditions harboring a significant number of activated CD30+ T cells are referred to as CD30+ pseudolymphomas.⁶ Atypical enlarged CD30+ T cells were observed in inflammatory and infectious disorders such as molluscum contagiosum, viral warts, pityriasis lichenoides, or drug eruptions.^{6,9,20} We did not find any reports on the presence of CD30+ T cells in LS. In reactive conditions, CD30+ T cells are usually found as single units or small

Table 2
Diagnostic Criteria for Atypical Intravascular CD30+ T-Cell Proliferation

1. Association with trauma, ulceration, and/or inflammatory processes
2. Intralymphatic accumulation of medium- to large-sized activated lymphocytes
3. Expression of T-cell markers and CD30 and lack of B-cell marker expression by the medium- and large-sized intravascular lymphocytes
4. No loss of T-cell markers (eg, CD3; except for CD7) and absence of Epstein-Barr virus (EBV) RNA or EBV-associated proteins in the atypically appearing CD30+ lymphocytes
5. Absence of monoclonal rearrangement of T-cell receptor β or γ genes
6. No indication for cutaneous or systemic lymphoma by staging examinations
7. Indolent course with complete resolution after regression of ulceration or inflammatory process; no development of lymphoma during follow-up

clusters in the background of small lymphocytes, neutrophils, eosinophils, and plasma cells. Usually, the stimulated blasts show a normal T-cell phenotype. The partial or complete loss of CD7, as observed in our case, is less specific for an aberrant T-cell phenotype compared with the loss of other T-cell-associated antigens indicative of lymphoma, since this phenomenon may be observed in inflammatory dermatoses. Molecular studies revealed polyclonal T cells in virtually all cases and therefore may represent a useful adjunctive diagnostic marker. In our case, no clonal T cells were detected by PCR and fragment analysis. Nevertheless, one has to keep in mind that monoclonal T cells can be found in LS specimens, and therefore detection of clonality in such a scenario may be prone to misinterpretation as a hint for malignancy.²¹ We propose diagnostic criteria for atypical CD30+ intravascular T-cell proliferation, as listed in **Table 2**.

In our case, the enlarged atypical CD30+ cells were located within lymphatic vessels, as underlined by expression of podoplanin by the endothelial cells lining the ectatic dermal vessels. The photomicrographs and descriptions of histologic findings in the other cases reported in the literature also suggest that the CD30+ cells are mostly located within lymphatic vessels. Therefore, the term *benign atypical "intralymphatic" CD30+ T-cell proliferation* may be more precise than employing the more general term, *intravascular T-cell proliferation*, as proposed by Ardighieri et al¹⁸ for a similar but widely CD30-negative intravascular T-cell proliferation in a cutaneous hemangioma. Pathogenetically, obstruction of lymphatics due to chronic inflammation with disrupted immune cell trafficking may result in the accumulation of activated CD30-positive lymphocytes in LS or chronic inflammation after trauma.²²

In conclusion, we present a case of benign atypical intravascular CD30+ T-cell proliferation occurring in the area of LS with ulceration. The intralymphatic large CD30+

T cells of the helper phenotype represent activated cells most probably trafficking between the area of chronic inflammation and the regional lymph nodes in a clinically inapparent mode. Pathologists and dermatopathologists should be aware of this rare and unusual finding to avoid misinterpretation as IVL.

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